Advances and future directions in management of prostate cancer

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Abstract Despite the high cure rates of patients diagnosed and treated with prostate cancer, there is still room for improvement in management of these patients. This includes the identification of patients at highest risk for progression, the usage of focal therapies in low risk disease, and the continued improvement on established modalities. Through these avenues, the morbidity associated with treatment for prostate cancer can be vastly reduced, and thus patient outcomes improved. This article reviews the current treatment modalities and future directions for the treatment of localised prostate cancer.

Keywords Prostate cancer · Future directions · Localised

Introduction

Worldwide, prostate cancer is the most common solid malignancy in men and the incidence is rising. In the past few decades, there has been a significant shift in patients who are diagnosed with prostate cancer. With the advent of widespread PSA testing, most patients are being diagnosed with cancer prior to detection of a palpable nodule. Through transrectal ultrasound (TRUS) guided biopsy, smaller cancers are being detected and undoubtedly some of these are clinically insignificant. Unfortunately, once patients have cancer which has spread outside the prostate, all therapies are palliative. The difficulty in treating prostate cancer resides in the fact that despite an incidence of almost 16%, only 2% of men will actually succumb to their disease [1]. Our ability to identify patients with high-risk disease with likely risk of progression is not reliable enough. Even with extended biopsy techniques, the percentage of patients with more aggressive tumour than that discovered on the biopsy still exceeds 30% [2].

Improved quality-of-life following local therapy for prostate cancer has driven many of the recent advances. Historically, urinary incontinence and sexual dysfunction accompanied treatment for prostate cancer. With the possibility of detecting clinically insignificant cancers, physicians are forced to walk the thin line between over-treatment with exposure to possible adverse quality-of-life, and performing curative therapies in the window of curability. With multiple methods for treating prostate cancer, pairing each patient with the correct treatment is the most difficult decision facing both the physician and the patient. This article is a review of recent advances in the management of prostate cancer, with a focus on surgical therapies, and potential future directions.

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Current advances in management options

Nomograms for risk stratification

Improvements in statistical analysis and large datasets of prostate cancer patients have produced several nomograms which can predict likelihood of aggressive prostate cancer. Initially, D'Amico and colleagues discussed the classification of patients into either low, intermediate or high risk groups [3]. The "Partin Tables," with their most recent update, discuss the likelihood of prostate cancer that being either extraprostatic or metastatic to the lymph nodes [4]. The UCSF-Capra score predicts likelihood of 5 years recurrence, and has been validated in outside cohorts [5, 6]. Perhaps the best known are the Kattan nomograms which discuss likelihood of cancer specific survival taking into account many preoperative values including PSA, digital rectal examination, age, biopsy pathology, early hormone therapy and method of diagnosis [7]. Usage of nomograms has improved the clinician's ability to identify patients at high risk for prostate cancer progression and death.

Active surveillance

There has been a substantial increase in low-risk patients being placed on active surveillance for the management of their cancer. Previously referred to as "Watchful Waiting," this option has become structured with regular protocols including repeat prostatic biopsy and routine follow-up visits. Clearly this is not the best option for all patients, but recent data suggests that in a highly selected group of patients, active surveillance could provide a safe alternative to radical local therapy [8, 9]. Caveats of this option include psychological distress, poor compliance, and possibly missing the window during which a cancer could be curable. Additionally, there is not a community standard for the appropriate follow-up schedule in these patients, creating many different protocols with potentially differing rates of effectiveness. Currently, data is not mature enough to evaluate this as long-term therapeutic option, however in select motivated patients this is emerging as a very attractive alternative.

Androgen deprivation therapy

Historically, androgen deprivation therapy (ADT) was considered a reasonable option for treatment of localised prostate cancer. Recently evaluation of patient outcomes for men on primary hormonal therapy for prostate cancer has demonstrated that these men are at significantly increased risks for cardiac related deaths. This trend is especially apparent in patients with a previous history of cardiac disease [10]. Overall survival showed no significant improvement with this therapy in several retrospective

studies of large cohorts, and this has forced the oncologists to re-evaluate the role of ADT in localised cancer. Therefore, only in select cases ADT is given as primary treatment for localised prostate cancer. In conjunction with external beam radiation therapy, 2 years of androgen deprivation is clearly advantageous [11]. In patients with positive lymph nodes following radical prostatectomy, addition of androgen deprivation improves survival [12]. However, current evidence points to the role of androgen deprivation as a part of multimodal therapy regimen in patients requiring secondary therapies.

Focal therapies

In an effort to decrease the side effects of radical local therapy for prostate cancer, focal therapies have been developed. These therapies are aimed at biopsy sites of prostate cancer. Cryotherapy, which involves freezing specific areas of the prostate with cooling probes, and high-intensity focused ultrasound (HIFU) are the two most widely accepted methods. These are attractive options to many patients due to the precision of the technology, and potential for diminished side-effects of incontinence and erectile dysfunction. Additionally, these can be completed in a single outpatient treatment session which is attractive to physician and patient alike.

In cryotherapy for localised prostate cancer the freezing probes are introduced into the prostate under ultrasound guidance, and the prostate is given either one or two freeze thaw cycles. Physicians can evaluate the efficacy of treatment in real-time mode using ultrasonography, and these images correlate well with cellular destruction. Many technical aspects are difficult; these include the prevention of damage to surrounding tissues due to the enlarging ice ball, achieving the -40°C required for tissue necrosis and identifying highly vascular "heat sinks" which may reduce efficacy. There have been early successes in the oncologic utility, as negative biopsy rates following treatment is high. In the United States a consortium of physicians has created a national database evaluating long-term oncologic success, and have demonstrated promising 5 years biochemical recurrence free survival [13].

HIFU uses hyperthermia to cause instantaneous and irreversible coagulative necrosis of the targeted tissue. *In vivo* and *in vitro*, HIFU has been demonstrated to effectively destroy prostatic cancers without increasing the risk of metastases. Due to the small focal zone, the surrounding tissues can be avoided and therefore the periprostatic nerves and continence mechanisms are theoretically spared. This can be used in conjunction with real time MRI imaging which may improve the ability to identify the malignant tissue. HIFU often requires prolonged urethral catheterisation following treatment secondary to prostatic "sloughing" which may cause obstruction [14].

Recurrence rates and morbidity associated with treatment plagued early reports on the use of this technology. However, in centres of excellence, the learning curve has been passed, and incidence of urinary incontinence and reported sexual function has been promising in these patients. Focal therapies are burdened by the fact that prostate cancer is typically multifocal, with several areas throughout the prostate exhibiting oncogenic changes. Additionally, as with all emerging therapies, long-term data has not matured in the cohort of patients treated with these technologies. As there is significant variability in the size of benign and malignant tumours, using focal therapies in larger prostates has proven very difficult. These might not be suitable for patients with benign prostatic growth in addition to malignant prostatic transformation [15]. There are very strong organising efforts behind these therapies with national patient database registries and well designed clinical trials evaluating efficacy. Promise in these therapies will rest in the ability to adequately treat cancers, and for their dissemination from the hands of experts into the community.

Technologies that have proven successful in other specialties such as ophthalmology and plastic surgery are also being tested in their ability to treat prostate cancer. Vascular targeted photodynamic therapy (PDT) is efficient in targeted destruction of tissue and requires the usage of a photosensitiser and laser light of a specific wavelength in the presence of oxygen. After absorbing the light, the photosensitiser transfers the energy to adjacent oxygen molecules, which results in reactive oxygen species and induction of cellular destruction. As the light is produced by a laser and delivered with fiberoptic technology, it can be delivered very precisely thus preventing damage to adjacent tissues. PDT has not been used as first-line therapy currently, but has shown to have good outcomes in patients with recurrence following treatment with radiation therapy. Phase II clinical trials are ongoing in patients with newly diagnosed cancer and shortly the results evaluating this as a future direction in prostate cancer therapy will be available [16].

Radiation therapy

Several forms of radiation therapy are currently available for treatment of localised prostate cancer including both convention external beam (XRT) and brachytherapy. These can be combined with hormonal therapy in high-risk patients, and this provides significantly improved outcomes in those cohorts. The ability of radiation oncologists to pinpoint the prostate and use conformal 3-D technology to follow minute motion of the gland has improved efficacy of radiation dosage. This prevents many of the adverse side-effects associated with periprostatic radiation exposure including gastrointestinal disturbances and urinary

complications [17]. Intensity modulated radiation therapy (IMRT) has been effective in improving oncologic outcomes as well. With the increased accuracy, dosage of radiation delivered to the prostate has been increased from 70 to 78 Gy with improvements in cancer cure rate. Brachytherapy, or placement of radioactive seeds into the prostate under ultrasound guidance is particularly effective in patients with low-to-moderate risk prostate cancer, and can be performed as an ambulatory procedure [18].

Radical prostatectomy

Radical prostatectomy is the definitive therapy for treatment of localised prostate cancer [3]. Patients undergoing radical prostatectomy have improved oncological outcomes compared with other modalities, however, the deterioration in quality-of-life occurs almost immediately. Therefore, the onus has been on the surgeon to improve outcomes in patients undergoing radical prostatectomy, and the advent of minimally invasive surgery appears to be the first step. Initially with strict laparoscopic techniques and currently using the Da Vinci Surgical System® (Intuitive Surgical, Sunnyvale CA), or “robotic” approach, this has quickly been adopted as a method of choice for improving outcomes.

Da Vinci (robotic) radical prostatectomy is the most common method for surgical removal of the prostate in the United States currently. While a randomised comparison to open prostatectomy hasn’t been done, nor is likely, systematically evaluating the current literature surrounding this procedure has provided several significant advantages to this technique. There has been much less blood loss with this procedure [19]. In fact, a recent evaluation of the medical complications of radical prostatectomy demonstrated significant reduction in patients undergoing a minimally invasive approach to cancer therapy [20]. While there is still controversy surrounding whether functional outcomes following robotic radical prostatectomy are improved, certainly the 10× magnified vision and endowristed movements provide the surgeon with increased control and precision surrounding the neurovascular pedicles along the prostate.

Surgical technique has continued to evolve with the technology, and several recent advensts are of particular importance. Through the improved visualisation created with the robotic system, nerve sparing techniques have been refined to preserve the lateral prostatic fascia, or the “Veil of Aphrodite” [21]. By creating an intrafascial plane along the lateral prostate, and extending this plane anteriorly, additional nerves and vasculature can be preserved thus improving postoperative sexual function. Improvement in understanding the lymphatic drainage of the prostate has led to increased lymph node yields, and removing the nodes which represent the primary landing zone for the prostate. This has been completed with incredible efficacy using

the da Vinci surgical system [22]. Even the requirement for a urethral catheter following radical prostatectomy has been challenged, and patients without a urethral catheter appear to have similar outcomes with improvement in perioperative discomfort [22].

Due to the nature of prostate cancer and disease progression, oncological outcomes are just beginning to mature in this population. The course of prostate cancer progression following recurrence has the median time to bony metastases at 8 years, and the vast majority of patients with localised disease will be cured with surgery. Therefore, due to the low incidence of progression, we can not accurately compare cancer specific survival in robotic and open patients. However, biochemical recurrence data is similar between studies evaluating patients undergoing minimally invasive and open surgical management [23]. At this point in time, we can conclude that robotic prostatectomy does not produce inferior oncological outcomes.

In an effort to improve cosmetic results and patient outcomes, single port laparoscopic approaches have been gaining popularity among laparoscopic surgeons. These approaches have been described for radical prostatectomy, with and without robotic assistance. Natural orifice endoscopic surgery (NOTES) has been described for other urologic surgeries, and likely progression to prostatectomy is likely on the horizon [24]. These techniques appear to be a new frontier in surgical management of prostate cancer. Whether these technologies will disseminate from academic centres to community practices or remain the techniques of a few skilled surgeons is yet to be seen.

Future directions

As management of prostate cancer has evolved significantly in the past decade, we can only hope to continue improving patient outcomes as we move forward. Perhaps first and foremost, we as physicians need to accurately identify those patients who will benefit the most from radical local therapy and treat them aggressively. The usage of PSA for detecting prostate cancer has come into controversy lately, and even its most ardent proponents have realised the limitations in PSA [25, 26]. Further screening methods, including the usage of free PSA, PCA3 and others have been tried, but these are not common place, and have faults of their own [27]. In order to optimise result and resources, the patients with clinically significant disease must be realised preoperatively.

Primary prevention of prostate cancer may also represent a direction for future management. There has been one large trial demonstrating the use of 5- α reductase inhibitors can prevent the detection of prostate cancer in men at risk [28], and further trials are ongoing. These medications prevent the conversion of testosterone to DHT, a more potent agonist for prostatic growth. Unfortunately, the

SELECT trial did not demonstrate any evidence that either Vitamin E or selenium prevent prostate cancer development [29]. Future trials focused on chemoprevention are being planned currently, and will hopefully reduce the burden of prostate cancer.

Conclusions

Despite the high cure rates of patients diagnosed and treated with prostate cancer, there is still room for improvement in management of these patients. Identifying the patients at risk for disease progression and aggressively treating them while preventing over-treatment and its side-effects are the next frontiers in management of prostate cancer.

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